THE INVENTION

The teachings of the instant application relate to generation, selection, and identification of negative-strand RNA viruses that have an impaired ability to antagonize the cellular interferon response, and the use of such viruses in vaccine and pharmaceutical formulations. In particular, the invention describes methods to propagate engineered or reassorted viruses for the generation of mutants with altered interferon (IFN) antagonist activity for formulation into vaccines. The genetically engineered mutants can contain deletions, truncations, or modifications to the NS1 gene that will result in an attenuated virus with a diminished or abolished ability of the NS1 gene to antagonize the cellular interferon response. The invention encompasses methods and substrates for the propagation of viruses with the desired phenotype (*i.e.*, low or no IFN antagonist activity) for vaccine formulations. Viruses with low or no IFN antagonist activities, although desirable for vaccine formulations, are difficult to propagate due to their attenuated phenotype. Prior art methods for propagating attenuated viruses, resulted in low yields and/or required the addition of agents that rendered the recovered viruses unsuitable for vaccine delivery. The present invention provides growth substrates which are IFN deficient that allow for the propagation of high concentrations of attenuated viruses with low or no IFN antagonist activities. The present invention provides for the first time, methods and substrates for propagating viruses with the desired phenotype, (*i.e.*, low or no IFN antagonist activity), in sufficient quantities and, in such a way, such that the propagated viruses are appropriate for use in vaccine formulations.

REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 23-40 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Mitsuhashi *et al.* (U.S. Patent No. 4,659,569; "Mitsuhashi") and Sasaki *et al.* (JP 59-29831; "Sasaki"). Briefly, the Examiner contends that Mitsuhashi and Sasaki teach that embryonated eggs under 10-days-old are susceptible to viral infection and replication, particularly influenza viruses. The Examiner does appreciate that, neither of the cited references teach the "specific viral strains" of the claimed invention, however, according to the Examiner, it would have been *prime facie* obvious to one of ordinary skill in the art at the time of the invention, to apply the teachings of the cited references to make the

composition of the claimed invention. According to the Examiner, one skilled in the art would have been motivated to do so because "it is notoriously old and well known in the art to propagate viruses in such eggs" and one would "reasonably expect the infected egg to yield replicated virus".

Applicants believe that the Examiner has overlooked the salient features of the claimed invention. Applicants claim suitable substrates for virus propagation (*e.g.*, immature embryonated eggs) and propagation of viruses suitable for vaccine formulations. In particular, Applicants teach for the first time, that immature embryonated eggs less than 10-days-old (*i.e.* six-days-old) provide a better growth substrate for attenuated viruses than older embryonated eggs (*e.g.*, 10 and 14-day-old embryonated eggs) which were the conventional substrates for vaccine production at the time of filing of the instant application. This result of the claimed invention is particularly surprising and unexpected because the allantoic cavity of immature embryonated eggs is very small and thus, not an obvious growth substrate to propagate viruses to high titers.

Mitsuhashi teaches methods for production of virus vaccines utilizing 10-day-old embryonated eggs. Mitsuhashi also describes the propagation of Newcastle disease virus in 8-day-old eggs.

Sasaki teaches a method for production of an inactivated influenza vaccine for pigs obtained by adding Macrogol, a polyethyleneglycol composition, to influenza viruses that are propagated in embryonated 9-11 day old egg allantois.

A finding of obviousness under Section 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere,* 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Moreover, to make a *prime facie* case of obviousness, there must be evidence that the ordinarily skilled artisan would be motivated to combine the references. *See, e.g., Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 375 (Fed. Cir. 1986); *In re Rouffet*, 149 F.3d 1350; 46 USPQ2d 1453 (Fed. Cir. 1998). It is not enough for the

components of the invention to be disclosed or suggested in different prior art references; there must be some motivation or incentive to put the components together. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 15 U.S.P.Q.2d 1321 (Fed. Cir. 1990).

In the present instance, the relevant inquiry is whether the cited art suggests using the immature embryonated eggs or the interferon deficient substrates for propagation of recombinantly engineered or reassorted negative-strand RNA viruses of the invention. Applicants believe for the reasons detailed below that the rejection under 35 U.S.C § 103(a) cannot stand and should be withdrawn. Neither of the cited references teach the unconventional IFN deficient substrates of the claimed invention (*e.g.*, the immature embryonated eggs less than 10-days-old, preferably 6-day-old, for the propagation of viruses). Neither Mitsuhashi nor Sasaki recognize or appreciate that immature embryonated eggs (*e.g.* less than 10 days old and preferably six-day-old) are a better substrate for the propagation of the genetically engineered or reassorted viruses with diminished IFN antagonist activities. Neither of the cited references teach propagating viruses that are recombinantly engineered or attenuated, and there is no teaching of the use of reassorted viruses with the desired phenotype, (*i.e.*, low or no IFN antagonist activity), for vaccine formulation.

The cited references, alone or in combination, fail to provide one of skill in the art at the time of the filing of the instant application, with any motivation to use immature embryonated eggs or interferon deficient substrates for the propagation of viruses with low or no IFN antagonist activity to high enough titres for vaccine production. In particular, the cited references, alone or in combination, fail to provide one skilled in the art to propagate recombinantly engineered, attenuated or reassorted viruses with low or no IFN antagonist activity. Finally, since the Applicants have demonstrated at least one unexpected benefit of the claimed invention as compared to the cited art, the claimed embryonated eggs and interferon deficient substrates of the invention for use in vaccine production are not rendered obvious over the cited art.

In view of the foregoing, the Applicants respectfully submit that the rejection under 35 U.S.C § 103(a) has been overcome and obviated and respectfully request that the rejections be withdrawn.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. Applicants believe that each ground for rejection has been successfully overcome or obviated, and that all of the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections is therefore respectfully requested.

Respectfully submitted,

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